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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,527	06/14/2002	Dirk Johannes Schaefer	0273-0004	4394

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,527	SCHAEFER ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-39,41-44 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-39,41-44 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/07 has been entered.

Applicant's amendments filed 1/11/07 to claim 36 have been entered. Claims 36-39 and 41-67 remain pending in the current application, of which claims 36-39, 41-44, and 67 are being considered on their merits. Prior art references not included with this Office action can be found in a prior action.

Claim Rejections - 35 USC § 102

The rejections of record under 35 U.S.C. § 102 are withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 103

The rejections of record under 35 U.S.C. § 103 are withdrawn in light of the claim amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36, 38, 41, 42, 44, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itay (1991, U.S. Patent 5,053,050) taken in view of Mikos (1996, U.S. Patent 5,522,895; reference A), Rosenthal et al. (1995, U.S. Patent 5,466,462; reference B), and Jakob et al. (WO 99/21497; and German-to-English translation). Regarding Jakob et al., the page and paragraph numbers in this rejection refer to the English translation.

Itay teaches a composition produced *in vitro* that comprises a biocompatible carrier material (*e.g.* a fibrin matrix) and chondrocytes that have been expanded and enriched in culture medium; the composition may be implanted into defective bones (Examples 1-3 and The Process). The composition of Itay can be produced in any shape, including cylindrical shapes (column 4, line 68) and the particular shape of the damaged area (column 5, lines 3-4), and in any size (Example 3).

Itay does not teach an *in vitro* composition comprising both cultured cartilage cells and cultured bone cells, said composition comprising cartilage cells on one face thereof and bone cells on the opposing face.

Mikos teaches seeding osteoblasts in growth medium onto a biodegradable polymer (column 4, lines 23-29), allowing the suspension to wick into the polymer foam (lines 29-33), and culturing the cells on the polymer to allow them to attach to the foam (lines 35-55). Mikos teaches that the culturing step allows the osteoblasts to secrete their own extracellular matrix, facilitating cell attachment and gradually eliminating the need for the polymer foam (column 4, lines 46-51). Mikos teaches that biodegradable polymers that form fibers are known in the art and include polyglycolic acid (column 3, lines 30-47). The composition of Mikos may take any desired anatomical shape according to the mold used to shape the polymer (column 3, lines 48-62).

Rosenthal et al. teach that fibrin and polyglycolic acid are functional equivalents in the tissue engineering and wound healing arts (column 1, lines 15-23).

Jakob et al. teach a composition comprising both a bone side and a cartilage side; the composition of Jakob et al. is a column of tissue that has been removed from a donor site at the articular face of a bone (page 2, paragraph 3; Figures 1, 5-7, 9, and 10). Jakob et al. also teach a composition comprising cartilage cells cultured *in vitro* on bone-replacement material (page 5, paragraph 3; page 16, paragraph 3; Figures 11 and 12). The composition of Jakob et al. may have a circular cross-section (page 11, paragraph 4; page 12, paragraph 4; and Figures 13-16) or may have any shape (page 15, paragraph 3).

It is noted that claim 36 recites "consisting essentially of." M.P.E.P. § 2111.03 clearly indicates that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). For the purposes of searching for and applying prior art under 35 U.S.C. §§ 102 and 103, **absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."** If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964) *et al.* Since the specification in this case does not particularly point out the basic and novel characteristics of the claimed composition, "consisting essentially of" in claim 36 has been interpreted as "comprising" for the purpose of art rejections. Furthermore, as discussed in a previous Office action, the claim limitations "cartilaginous substance" and "bone substance" are not provided with limiting definitions (see page 5, lines 11-17 and 21-29 of the as-filed specification); rather, these terms include all non-cellular components of cartilage and bone, respectively. It is not clear what components may and may not be included in the claimed composition without materially affecting its basic and novel characteristics.

A person of ordinary skill in the art would have had a reasonable expectation of success in combining the *in vitro* cartilage construct of Itay and the *in vitro* bone construct of Mikos because Rosenthal et al. teach that the biodegradable polymers on which each construct is based are functional equivalents for each other; therefore, the cartilage construct of Itay could be modified to include bone cells on one side, and the bone construct of Mikos could be modified to include cartilage cells on one side. The skilled artisan would have been motivated to combine the teachings of Itay and Mikos because Jakob et al. teach that compositions that have bone tissue on one side and cartilage tissue on the opposite side provide efficient repair of defects on the articular face of bone joints (page 15, paragraph 2, *inter alia*).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the *in vitro* bone construct of Mikos and the *in vitro* cartilage construct of Itay to yield a composition comprising cultured cartilage on one side and cultured bone on the opposite side because Jakob et al. teach that compositions so configured may be implanted into the articular portions of bones to effectively treat defects.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant's arguments have been considered to the extent they read on this new ground of rejection. Applicant alleges that Itay does not teach an *in vitro* construct comprising cultured chondrocytes and cultured osteocytes in the claimed configuration (Reply, pages 9-12). Applicant alleges that Jakob et al. do not teach an *in vitro* joint

construct comprising cultured chondrocytes and cultured osteocytes immobilized on firmly connected opposite sides of a biocompatible material (Reply, page 12, last paragraph, through page 13, first paragraph). Applicants allege that the composition of claim 36 consists essentially of cultured osteoblasts and/or osteocytes, which is not taught by Jakob et al. (Reply, page 13, paragraph 3). Applicants allege that natural bone tissue is not identical to the instant invention (Reply, page 13, past paragraph, through page 17, last paragraph), specifically arguing that the exemplified compositions are distinct from bone (pages 15-17). Applicant alleges that Mears, Vacanti et al., and Caplan do not teach the claimed construct (Reply, page 18). These arguments have been fully considered, but they are not persuasive.

First, as a matter of formality, the examiner requests that applicant refrain from submitting color drawings within future arguments. According to the M.P.E.P., the only provision for the use of color in patent prosecution is in color notations in paper files and in color drawings that have been approved by petition to the Office and accompanied by a fee. Including color drawings in the arguments increases processing time both in the mailroom and by the examiner. Applicant's cooperation in this matter is appreciated.

This new rejection recognizes the amendments to the claims and is not over any one reference individually, but rather over Itay (which teaches cultured cartilage tissue) taken in view of Mikos (which teaches cultured bone tissue, which Itay lacks), Jakob et al. (which provides motivation to produce a composition comprising both engineered bone and engineered cartilage on opposite sides of a single construct), and Rosenthal et al. (which teaches that the cells of Itay and Mikos would have been reasonably

expected to grow on a single substrate, since the person of ordinary skill in the art would have recognized that the substrates employed by Itay and Mikos are functional equivalents).

The evidence set forth by applicant as to the distinction between natural and engineered bone is noted; however, the limitations discussed in this evidence are not recited in the claims. For example, the claims do not limit the carrier material to tricalcium phosphate (as on page 15 of the Reply) or hydroxyapatite-collagen (as on page 16), so the discussion of these limitations is not relevant to the claims under consideration. As to the "consisting essentially of" limitation in claim 36 and applicant's assertions at page 13 of the reply, the specification does not particularly point out that any of the components in the last paragraph of page 13 would materially affect the basic and novel characteristics of the composition. Furthermore, claim 36 is drawn to a composition "comprising" a joint side that "consists essentially of" particular components and an anchor side that "consists essentially of" other components, so the claim does not preclude the presence of the components discussed in the reply.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Itay, Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Goldstein et al. (1999, U.S. Patent 5,962,427; reference C) and Vacanti et al. (1998, U.S. Patent 5,804,178; reference D).

The teachings of Itay, Mikos, Rosenthal et al., and Jakob et al. are relied upon as above. Furthermore, Itay teaches that the *in vitro* cartilage composition may include

progenitor cells of mesenchymal origin, bone marrow stromal cells, or any undifferentiated mesenchymal cells (column 3, lines 35-46) and may include additional active agents including serum (column 3, lines 47-52).

Itay, Mikos, Rosenthal et al., and Jakob et al. do not teach or suggest including a growth factor that promotes angiogenesis or including endothelial cells or their progenitors in the composition.

Goldstein et al. teach that including DNA encoding vascular endothelial growth factor (VEGF) in an implanted biocompatible matrix promotes angiogenesis at the implant site by transfecting nearby cells (column 2, lines 21-36; column 14, lines 13-45; and column 24, lines 7-29). The matrix of Goldstein et al. may be any biodegradable matrix (column 11, line 19, through column 14, line 4), including PGA (column 12, line 35). Goldstein et al. also teach administering recombinant VEGF protein (column 2, line 42, through column 3, line 31).

Vacanti et al. teach implanting endothelial cells in a biodegradable matrix such as PGA (Abstract; column 3, lines 5-41; column 4, lines 52-57; column 5, lines 49-50).

A person of ordinary skill in the art would have had a reasonable expectation of success in including either pro-angiogenic growth factors (such as VEGF) or cells carrying cDNAs therefor or endothelial cells *per se* (which are required structural components of blood vessels) in the composition of Itay in view of Mikos, Rosenthal et al., and Jakob et al. because Itay suggests including additional cell types and additional active agents and because Goldstein et al. and Vacanti et al. teach that VEGF protein, VEGF cDNA, cells transfected with VEGF cDNA, and endothelial cells may be

implanted using a biocompatible matrix equivalent to those employed by Itay and Mikos. The skilled artisan would have been motivated to include endothelial cells and/or pro-angiogenic growth factors for the expected benefit of increasing the degree of vessel formation around the implant after it has been placed into a recipient, thus improving the implant's ability to incorporate into the recipient's body.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include the pro-angiogenic factors of Goldstein et al. or the endothelial cells of Vacanti et al. in the composition of Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. because Goldstein et al. and Vacanti et al. teach that these components improve angiogenesis upon implantation of such a composition, thus increasing the chance that the composition successfully engrafts in a patient.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant's arguments have been considered to the extent they read on this new ground of rejection. Applicants rely on arguments traversing the above rejection to traverse this rejection. Therefore, the response set forth above to arguments also applies to this rejection.

Claims 39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itay, Mikos, Rosenthal et al., and Jakob et al. as applied to claims 36, 38, 41, 42, 44, and 67 above, and further in view of Wevers (1981, U.S. Patent 4,246,660) and Dunn et al. (1995, *Journal of Biomedical Materials Research* 29: 1363-1371).

The teachings of Itay, Mikos, Rosenthal et al., and Jakob et al. are relied upon as above.

Itay, Mikos, Rosenthal et al., and Jakob et al. do not teach or suggest compositions comprising ligaments or joint capsules.

Wevers teaches a prosthetic ligament device comprising an elastic synthetic woven material, the device being securable to bones by use of bone screws (claim 1 and Figures).

Dunn et al. teach a ligament analog prepared by seeding collagen scaffolds with fibroblasts that approximates the structure and strength of native ligament tissue. The artificial ligament of Dunn et al. remains viable after implantation into a joint.

A person of ordinary skill in the art would have had a reasonable expectation of success in connecting the parts of the bone replacement of Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. with the artificial ligaments of Wevers and Dunn et al. because the artificial ligaments are disclosed as having properties similar to native ligament tissue. The skilled artisan would have been motivated to connect multiple compositions of Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. with the ligament compositions of Wevers and Dunn et al. for the expected benefit of strengthening the replaced joint. The artificial ligament of Wevers in particular is disclosed as having elastic properties closely approximating natural ligament tissue (Figures 2 and 3), so joining the joint replacement elements with the ligament of Wevers would more closely simulate a natural joint (see Abstract).

It would therefore have been obvious to a person of ordinary skill in the art to connect multiple compositions of Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. with ligament compositions in order to stabilize the replacement joint and to simulate more closely the natural properties of the joint.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants rely on arguments traversing the above rejections over Itay taken in view of Mikos, Rosenthal et al., and Jakob et al. et al. to traverse this rejection (Reply, page 20). Therefore, the response set forth above to arguments also applies to this rejection.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart